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THE PROBLEMS IN THE MODELLING OF INERT GAS KINETICS

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Abstract

The models used to describe the kinetics of inert gases during underwater diving are inadequate. Medical practitioners and scientists interested in such diving have attempted to quantitatively describe the behaviour of nitrogen in compressed air diving since 1908, with little success. The problems encountered during this diving research are relevant to anaesthesia theory and practice.

Introduction

Although inert gas kinetics become complex if bubbles form, the "inertness" of these gases should make their uptake, distribution and elimination simpler to model than gases and drugs which are metabolised. The history of these inert gas models however is that they describe events poorly. Indeed, the limited success of decompression schedules (since the first was introduced in 1908)[1] in diving, caisson work and aviation is relevant to anaesthesia theorists because it demonstrates the unsatisfactory nature of available models of inert gas kinetics. Given this recorded history of diving research and the perfusion-solubility bias of current theories of anaesthesia gas, vapour and drug kinetics, it is difficult to escape the conclusion that there has been little "cross-fertilisation" of ideas between the two disciplines to date.

A review of inert gas kinetic models is consequently presented here to demonstrate the lessons available (problems encountered) to anaesthesia from diving research. This will take the form of discussing these kinetics in the context of a compressed air dive to 30 metres of seawater (msw) depth. A similar, or identical. discussion would have resulted if a caisson worker or space-walking astronaut or patients receiving N_2O anaesthesia had been considered.

The requirement of an inert gas model

The objective of an inert gas model in diving is to develop a decompression program that will prevent decompression illness. This will require the following to be defined and then modelled:

a   the factors that influence the uptake of the inert gas into tissues during the dive (relevant to anaesthesia);

b   the factors that influence the elimination of the inert gas from tissues during and after the dive (relevant to anaesthesia); and

c   the conditions that must exist before bubbles form, as a limit to, or controller of the decompression (not usually relevant to anaesthesia).

Uptake of inert gases in an air dive to 30 msw

As the diver swims down or is lowered to 30 msw (400 kPa or 3040 mm Hg) breathing compressed air, the inspired nitrogen tension (PiN_2) will increase as predicted by Dalton[2] (Equation 1).

$$P_iN_2 \begin{aligned} &= P_{amb}.F_iN_2 \\ &= 400 \; kPa.0.8 \\ &= 320 \; kPa \end{aligned} \qquad \text{Eq.1}$$

where P_{amb} is the ambient pressure and F_iN_2 is the inspired nitrogen fraction. All published models assume that the alveolar (PAN_2) and arterial (PaN_2) nitrogen tension will also be at 320 kPa. The intrinsic assumptions here therefore include that respiration is not rate-limiting and that there is no significant venous admixture to arterial blood. However, following the withdrawal of an anaesthetic gas or during and after a decompression, inspired gas tensions will vary from alveolar and arterial tensions. Also at great depth, respiration and gas diffusion will be limited by gas density.[2] Nevertheless, the presumption that inspired, alveolar and arterial gas tensions are approximately equal is generally true and constitutes a small "error" in comparison to others described below.

The rate at which any given tissue will achieve a nitrogen tension (P_tN_2) in equilibrium with PaN_2 (320 kPa) will be determined variously by:

a   the tissue perfusion;

b   the relative solubility of N_2 in blood and in the tissue;

c   the diffusion of N_2 into the extra- and intracellular fluid of the tissue; and

d   the local tissue temperature, carbon dioxide tensions and work (which will influence perfusion, solubility and diffusion).

No model currently exists to account for all these factors and their potential interactions.

The majority of models, back to 1908, assume that uptake is determined only by tissue perfusion and relative solubility.[3] A single function exponential is used to calculate the P_tN_2 at a specific time (T) (Equation 2).

$$Eq.2.$$

where 80 kPa is the P_tN_2 on leaving the surface, 320 kPa is the PaN_2 on reaching 30 msw, Q is the blood supply to the tissue, and $\alpha\beta$ and αt are the solubility of N_2 in the blood and tissue respectively. Obviously, for a specific tissue, a fixed half-life $T_{1/2}$ can be ascribed.

The strength of this model is its simplicity. The major weakness is that the rate of actual uptake of N_2 into tissues has little in common with that predicted by the model.[4] In part, this failure is not surprising given the inherent ignorance of diffusion in the model[5] and the observation that most tissues have intermittent local perfusion.[6] It is clear that any uptake calculated from Equation 2 is based on the assumption of "instantaneous" diffusion of gases throughout the tissues (i.e. within a "circulation-time") and of continuous blood flow. Such an assumption may only be appropriate for small non-polar gases and for well perfused tissues such as the brain.

The only other significant alternative has been that proposed and used by the British researchers, Hempleman[3] and Hills.[5] Their argument is that gas uptake is reasonably described by considering diffusion alone (ie. a bulk-diffusion model based on the PaN_2 and the square root of time). There are no data to support either this theory (which arose from an empirical observation that a bulk diffusion model resulted in a reasonable prediction of the decompression programs employed by the United States Navy) or the consequent decompression schedules. Again, reality is poorly described (quantitatively) by these "diffusion" models. This is not surprising given the obvious limits on gas uptake that arise from perfusion and solubility and the observation that the United States Navy decompression programs studied by Hempleman[3] and Hills[5] often result in decompression illness.

Why is there no comprehensive model that considers relevant perfusions, solubilities and diffusion? The likely explanation is that the resultant model is difficult to manage. Also, some of these factors are reasonably unpredictable (local perfusion), unmeasurable (diffusion coefficients for gases in intracellular fluid) and inter-related (eg. an increase in temperature will increase some tissue perfusion, reduce the solubility of the gas in the tissues and simultaneously increase the rate of gas diffusion, such that an increase in tissue temperature may increase the uptake of an insoluble gas like helium and conversely decrease the uptake of a soluble gas like nitrogen).

Thus, while the phenomena that influence gas uptake are reasonably identified, 85 years of modelling has not resulted in an accurate quantitative description.

Elimination of inert gases during and after an air dive to 30 msw

A return to the surface will cause the P_iN_2 to return to 80 kPa and a consequent decrease in PAN_2 and PaN_2. Nitrogen will exit tissues until the P_tN_2 is restored to 80 kPa. Again, tissue perfusion, gas solubility, gas diffusion, tissue temperature, tissue carbon dioxide tensions and local tissue work will influence this elimination. Almost all models used and in use describe inert gas elimination as a mirror image of uptake. This gives an even worse "fit" than the determination of uptake as, for reasons that are not yet understood, inert gas elimination is much slower than uptake.[7] One or two models have tried to allow for this by deriving elimination kinetics as a 1.5 times slower function of uptake.[3,7] Unfortunately, this is a gross underestimate. For example, it takes several days to mass-balance the N_2O excreted after a brief exposure to this gas.[8]

It is possible that no gas is inert and that they all variously become "involved" in biological processes. In contrast, theorists have assumed that inert gases "passively" enter solution in tissues in proportion to the tissue gas tensions as estimated by Henry's Law.[2]

Inert gas elimination from tissues into blood becomes even slower still if bubbles form as much of the tissue gas will diffuse into the bubbles.[3,9,10] This is a fundamental observation; but, despite its critical relevance to repeated diving exposures and the development of decompression illness, is not incorporated in any existing model (presumably because the necessary mathematical model is extraordinarily complex[11]).

The formation of bubbles

Assuming that some estimate of gas uptake and elimination can be achieved, decompression can only proceed adequately if bubble formation is avoided. What then, are the conditions for bubbles to form? Using a Gibbs Free Energy construction,[12] the bubble energy (E_B) required for a spherical bubble to form in a compartment is equal to the sum of the energy needed to overcome surface tension ($E\gamma$) and for gas to come out of solution (E_{SOL})(Equation 3).

$$Eq.3.$$

where r is the radius of a spherical bubble and γ is the surface tension of the tissue liquid. Even if values of

surface tension measured in lung surfactants (eg. 8 dynes/cm) and not in plasma (eg. 45 dynes/cm) are used, the $E\gamma$ needed for a bubble to form would require a relative decompression of about 1000:1. Instead, a decompression of only 1.4:1 can be shown to cause bubbles in divers.[3] There is then a gross inequity between theory (models) and observation. Although this disparity might be explained by the effect of tribonucleation and shearing of tissue places (to create relative vacuums), surface defects in tissues and vessels (where the surface tension pressure acting on the "forming" bubble will be minimised) and the ongoing formation of bubble nuclei (these may only exist for picoseconds but will reduce the energy required for stable bubble formation by acting as "seeds");[13] again, theory (models) and quantitative reality are at variance.

Finally, the relationship between P_tN_2 and P_{amb} (the final component of Equation 3) that will cause a nitrogen based bubble to form has been debated without consensus since 1908. This relationship has been described as everything from a constant ratio,[1] to a variable ratio,[3] to a constant difference[3] and to a variable difference.[14] This uncertainty continues because the time of initial bubble formation can not be precisely determined, by either the time of development of symptoms (known to occur after mobile bubbles can be identified in the veins)[15] the ultrasonic detection of mobile venous bubbles ("known" to occur after stationary bubbles form in tissues). Emergent acoustic techniques may help to resolve this dilemma. Overall, it is likely that N_2 based bubbles will form whenever P_tN_2 exceeds P_{amb}.

Nevertheless, even assuming that acoustics will solve this problem, the modern theorist will still be faced with an old riddle, the intrinsic desaturation of tissue and venous blood relative to P_{amb} that results from the conversion of less soluble oxygen to more soluble carbon dioxide, and the effect that this desaturation will have on gas kinetics and bubble formation.[13] In anaesthesia, the breathing of higher than "normal" oxygen fractions will increase this degree of desaturation.

Since the first observation of decompression illness suddenly developing in a diver during a decompression stage (i.e. not actually undergoing decompression at the time) when the breathing gas was changed,[16] it has also been argued that changing the breathing gas may induce bubbling if the gases have widely differing diffusion coefficients. This has now been refined to differing net flux rates (where gas flux is a product of both gas diffusion and solubility). Observations in vivo suggest that changing from air to rapidly fluxing gases such as N_2O (and oxygen) will expand existing bubbles, but will not, fortunately for existing anaesthesia practice, provoke de-novo stable bubble formation.[17,18] Nevertheless, theoretically and anecdotally,[19] N_2O should not be administered to someone who has been compressed air diving within the last month as it may precipitate decompression illness (by causing pre-existing bubbles to grow).

Conclusions and recommendations

Clearly, there is a need for a comprehensive model of inert gas kinetics. In the interim, two practical recommendations can be made. Firstly, the choice of a decompression schedule for diving (ie. a method of practice) should be based on the demonstrated performance of that schedule and not on the attraction of the underlying inert gas model. Secondly, the real need at present is not for the production of more simplistic models of such inert gas kinetics, but rather for an accumulation of objective data to enable eventual definitive modelling.

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Key Words

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THE RETRIEVAL OF DIVING INJURIES IN NEW SOUTH WALES
A RETROSPECTIVE REVIEW OF TWO YEARS PRACTICE

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Abstract

The only medical recompression facilities available in NSW in case of decompression illness (DCI) are located in Sydney. Many cases must travel considerable distance to reach definitive treatment. A sophisticated network of retrieval facilities exists in NSW using road, fixed wing and helicopter transport platforms. Criticism has been generated over the use of helicopters for this purpose both with respect to altitude stress and vibration characteristics. While the issue of vibration as a possible deleterious influence on outcome seems to have settled somewhat with the advent of the twin engine machine, the possibility that retrieval at altitude will correlate with poor outcomes remains unresolved.

The interval between injury and recompression and the altitude at which any retrieval takes place are usually accepted as important factors of prognostic significance. This review examines the relationship between time to recompression, mode of transport and outcome for 107 consecutive cases of DCI seen at this unit.

Overall, 27% of cases failed to recover fully on final assessment. These figures are broadly consistent with those previously quoted in Australasia.

There was no statistically significant evidence for improved outcome as a function of shortened interval from symptom onset to recompression. Similarly, there is no evidence for the efficacy of one transport mode over another. No attempt was made to relate severity of injury to outcome for non-CAGE cases, although there is often assumed to be a correlation.

All but one of the cases labelled "Acute Neurological DCI of the CAGE Type" were transported by helicopter. That these cases recovered fully to a similar extent as those of less dramatic presentations may indicate that both early presentation and low level helicopter retrieval will prove positive factors for full recovery in the more exhaustive prospective study underway at this unit.

Introduction

Recreational diving is an activity practised widely along the coast of NSW. The only medical recompression facilities available in the State in case of injury are located in Sydney at The Prince Henry Hospital and the Naval facility at HMAS PENGUIN. Consequently, many patients suffering from decompression illness (DCI) must travel long distances to reach definitive treatment.

A sophisticated network of retrieval services has developed in NSW using road, fixed wing and helicopter transport and these facilities are commonly used for the medical retrieval of diving injuries. The choice of the most appropriate transport can prove difficult. This is particularly true with respect to DCI where minimisation of both the time to recompression and the altitude stress experienced are generally accepted as of great prognostic